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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,951	10/13/2000	Jeffrey I. Cleland	M-9177-US	8871

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BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610

EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	14

DATE MAILED: 09/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,951	CLELAND ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,20-23,25-31 and 33-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,20-23,25-31 and 33-36* is/are rejected.

7)☒ Claim(s) *37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 17, 20-23, 25-31 and 33-37 are pending.

Applicants' response filed on July 3, 2003 (Paper No. 23) is acknowledged and has been fully considered. Thus, claims 17, 20-23, 25-31 and 33-37 are examined.

Rejection(s) Withdrawn

Claim Rejections - 35 USC § 102 and 103

2. The previous rejection of claims 21-23, 26, 27 and 34 under 35 U.S.C. 102(a) as being anticipated by Pierre *et al.* (Fr 2,778,847, November 1999), is withdrawn in view of applicants' response at page 2 in Paper No. 23; and, the previous rejection of claims 17, 20, 21-23, 26-29, 34 and 35 under 35 U.S.C. 103(a) as being unpatentable over Pierre *et al.* (Fr 2,778,847, November 1999) taken with Mathiowitz *et al.* (U.S. Patent 5,985,354), is withdrawn in view of applicants' response at page 3 in Paper No. 23.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-31, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an injectable formulation comprising hyaluronic acid in physiological buffer and particles containing a biologically active polypeptide (e.g., hormone, and growth factor) and a biocompatible polymeric matrix such as poly(lactide-co-glycolactide) (PLGA), wherein the biocompatible polymeric matrix is defined; or an injectable formulation

containing hyaluronic acid in physiological saline or buffer and a microsphere containing a biologically active polypeptide dispersed in an identified polymeric matrix as indicated in the prior art, does not reasonably provide enablement for an injectable formulation containing hyaluronic acid in physiological buffer and particles containing a biologically active agent and a biocompatible polymeric matrix, where the biologically active agent and the biocompatible polymeric matrix are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 21-31, 33 and 34 are directed to an injectable formulation containing hyluronic acid in physiological buffer and particles containing a biologically active agent and a biocompatible polymeric matrix. The specification, however, only discloses cursory conclusions (pages 3-4) without data supporting the findings, which state that the invention describes a formulation suitable for injection contains an effective amount of a biologically active agent in the form of particles, coated onto particles, or dispersed in the particles, and an injection vehicle of hyaluronic acid. There are no indicia that the present application enables the full scope in view of the injectable formulation as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the

art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the biologically active agent and the biocompatible polymeric matrix in the formulation, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification describes the injectable formulation containing sodium hyaluronate as the injection vehicle mixed with anti-VEGF Fab PLGA microspheres, Nutropin Depot, VEGF microspheres, VEGF/heparin microspheres and NGF microspheres (Examples 1-7), however, there are no working examples indicating the preparation of the injectable formulation using other types of biologically active agents than polypeptide and various polymers as biocompatible polymeric matrix.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., McGinity *et al.*, US Patent 5,288,502; Cleland *et al.*, US Patent 6,113,947) teaches an injectable formulation containing hyaluronic acid in physiological saline or buffer and a microsphere containing a biologically active polypeptide such as NGF dispersed in PLGA or poly(lactic acid) matrix, however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the preparation/use of injectable formulation using various types of biologically active agents and various polymeric matrices to be considered enabling for the claimed variant.

(4). Predictability or unpredictability of the art:

The specification has shown injectable formulation containing sodium hyaluronate as the injection vehicle mixed with polypeptide microspheres (Examples 1-7). However, the specification has not demonstrated the preparation of injectable formulation using various types of biologically active agents and various polymeric matrices, since the preparation for the formulations containing various biologically active agents are not sufficiently described, the effects of these injectable formulations are not predictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to an injectable formulation containing hyaluronic acid in physiological buffer and particles containing a biologically active agent and a biocompatible polymeric matrix. The specification indicates an injectable formulation containing sodium hyaluronate as the injection vehicle mixed with various polypeptide microspheres such as VEGF microspheres, VEGF/heparin microspheres and NGF microspheres (Examples 1-7). However, the specification has not demonstrated the making and use of injectable formulations containing various types of biologically active agents and various polymeric matrices. There are no working examples indicating these formulations containing various biologically active agents in different polymeric matrices are suitable for injection using gauge-23 or smaller needles. Since the specification fails to provide sufficient teachings on the making of various injectable formulations, nor demonstrates the formulations are suitable for injections using gauge-23 or smaller needles, it is necessary to carry out further experimentation to assess the effects of various injectable formulations.

(6). Nature of the Invention

The scope of the claims encompasses injectable formulations containing hyaluronic acid as the injection vehicle and particles containing various biologically active agents and various biocompatible polymeric matrices, but the specification does not demonstrate the preparation and the effects of various injectable formulations. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the effect of injectable formulation is unpredictable, and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the injectable formulations containing various biologically active agents and various biocompatible polymeric matrices.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 20-23, 25-27, 30, 31, 33, 34 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 21-23, 25-31, 33, 34 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the specification appears to define hyaluronic acid (see page 4, lines 21+) as part of or as a biologically active agent (see the definition proffered at page 6, lines 10+ of the current specification). Thus, claim 21 and claims dependent thereof are indefinite as to whether hyaluronic acid is or is not part of an biologically active agent having in vivo activity, typically an activity that confers therapeutic, prophylactic, and/or diagnostic utility given the

definition at page 4 of hyaluronic acid being found in the extracellular matrix of connective tissue. Thus, in claim 21, is item (a) included in item (b)(i) and/or (b) (ii)? Claims 22, 23, 25-31, 33, 34 and 36 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicants indicate claim element (a) specifies "hyaluronic acid dissolved in a physiological buffer", and claim element (b) specifies particles, comprising (i) a biologically active agent, and (ii) a biocompatible polymeric matrix"; and the claim differentiates spatially a biologically active agent, which is situated as part of the particles, from hyaluronic acid, which is outside the particles. The response has been fully considered, however, the argument is not found persuasive because the claim does not indicate either the biologically active agent or the biocompatible polymeric matrix excludes the hyaluronic acid, and the specification indicates hyaluronic acid is a biologically active agent or a biocompatible polymeric matrix, and thus, it is not clear whether hyaluronic acid is included in the claim element (b) or not.

6. Claim 20 recites the limitation "a biologically active agent", which does not further limit claim 17 because claim 17 recites a "biologically active polypeptide".

In response, applicant indicates claim 20 recites "a biologically active agent", since it begins with "a", the claim is a sufficient antecedent basis, the argument is not fully persuasive because the independent claim recites "a biologically active polypeptide", which has a narrower scope than "a biologically active agent" cited in the dependent claim.

7. Claim 31 is indefinite because of the use of the term "the polymeric matrix comprising the biologically active agent". The term "the polymeric matrix comprising the biologically active agent" renders the claim indefinite, it is not clear how the polymeric matrix comprises the

biologically active agent since claim 17 recites the polymeric matrix and the biologically active agent are contained in the particles, the claim does not indicate the polymeric matrix comprises the biologically active agent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 17, 21, 25-29 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by McGinity *et al.* (US Patent 5,288,502, February 22, 1994).

McGinity *et al.* teach a preparation of multi-phase polymeric microspheres containing a molecular compound dispersed in a polymeric matrix and having particle size about 150 microns can be administered intramuscularly (Fig. 1, column 8, lines 48-62), wherein the molecular

compound can be a water soluble drug or protein (e.g., epidermal growth factor, LHRH, monoclonal antibody, column 6, lines 21-41; claims 28, 29 and 35) in a microemulsion of a fixed oil and an aqueous solution of microspheres (column 4, line 61-column 5, line 2), a biodegradable polymer such as poly(lactic acid) (PLA) and poly(lactide-co-glycolide) (PLGA) is used a polymeric matrix (column 6, line 59-column 7, line 2; claims 25-27), and some modification of the preparation of microspheres can be made, e.g., the pH of the aqueous phase containing the water soluble drugs can be adjusted using acid or phosphate buffer and a stabilizing agent such as hyaluronic acid can be added to enhance the stability of the protein (Example 7, claims 17 and 21).

9. Claims 17, 21, 23, 25-29, 34 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Cleland *et al.* (US Patent 6,113,947, filed June 13, 1997).

Cleland *et al.* teach a nerve growth factor (NGF) microencapsulation composition having controlled release characteristics, wherein NGF is dispersed in a polymeric matrix of microspheres, microparticulates and microcapules (column 2, lines 8-67; column 4, line 62-column 5, line 2; claims 28 and 29) and the microspheres are sieved to about 20-90 microns for injecting intramuscularly (column 19, lines 38-45; column 19, line 63-column 20, line 4; column 23, lines 53-63), and a biodegradable polymer such as a copolymer of lactic acid and glycolic acid (PLGA) is used a polymeric matrix (column 4, lines 24-32, Example 1; claims 25-27). The preferred injectable sustained-release preparation can be formulated with a viscous physiologically acceptable solution including a dispersant such as sodium hyaluronate, a preservative, an isotonizing agent such as NaCl, and a local anesthetic to provide an aqueous suspension (column 19, lines 47-62, claims 17, 21, 23, 34, 35).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 17, 20, 21, 23, 25-29, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleland *et al.* (US Patent 6,113,947) in view of syringe section (page T515) of Aldrich catalog (1996-1997).

Cleland *et al.* teach a nerve growth factor (NGF) microencapsulation composition having controlled release characteristics, wherein NGF is dispersed in a polymeric matrix of microspheres, microparticulates and microcapules (column 2, lines 8-67; column 4, line 62-column 5, line 2; claims 28 and 29) and the microspheres are sieved to about 20-90 microns for injecting intramuscularly (column 19, lines 38-45; column 19, line 63-column 20, line 4; column 23, lines 53-63), a biodegradable polymer such as a copolymer of lactic acid and glycolic acid (PLGA) is used a polymeric matrix (column 4, lines 24-32, Example 1; claims 25-27), and the preferred injectable sustained-release preparation can be formulated with a viscous physiologically acceptable solution including a dispersant such as sodium hyaluronate, a preservative, an isotonizing agent such as NaCl, and a local anesthetic to provide an aqueous suspension (column 19, lines 47-62, claims 17, 21, 23, 34, 35). However, Cleland *et al.* does not disclose the type of syringe needle used for injection. The Aldrich catalog shows a 23-gauge syringe needle has an inside diameter of 0.318 mm (318 microns), which is suitable for injection of the particulate preparation with particle size of 5-200 microns (claim 20). At the time of

invention was made, it would have been obvious to one of ordinary skill in the art to administer the microsphere preparation containing NGF to a patient as taught by Cleland *et al.* using a syringe of 23-gauge needle as indicated in the Aldrich catalog because one of ordinary skill in the art would have been motivated to deliver the formulation using the needles having the right gauge, e.g., 23-gauge or smaller. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

11. Claim 37 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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August 28, 2003